REMARKS

These remarks are in response to the Office Action mailed August 11, 2003. The specification has been amended to delete the browser-executable hyperlink found in paragraphs 140, 162, and 204. Claim 1 has been amended to more particularly define Applicants' invention. Thus, the amendments introduce no new matter. Claims 1-15 are pending.

Responsive to the Examiner's objection to the drawings, corrected formal drawings are filed herewith as Exhibit B.

A. Rejection Under 35 U.S.C. § 112, First Paragraph (Written Description)

The rejection of claims 1-3, 5, and 6 under 35 U.S.C. § 112, first paragraph, as containing subject matter which allegedly was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention, is respectfully traversed.

The burden of demonstrating that the claims are allegedly not supported by an adequate written description falls on the Examiner. *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976). In this case, the Examiner has provided insufficient evidence to call into question the written description set forth in the present application. Accordingly, for the following reasons, it is respectfully submitted that the Examiner has not met the burden of demonstrating an alleged lack of written description for the claimed invention.

Applicants respectfully disagree with the Examiner's assertion that the specification allegedly contains insufficient written description to support "for screening for the bioactivity of a candidate compound toward a group of related target proteins in a

proteomic mixture of proteins from a cell, employing a probe." In contrast to the Examiner's assertion, it is respectfully submitted that methods for screening for bioactivity of a candidate compound are described throughout the specification. For example, at page 10, paragraph 38, the specification describes, as follows,

> The combinatorial chemical libraries of the present invention are useful as screening tools for discovering new lead structures through evaluation of the compounds in the library across an array of biological assays, including the discovery of selective inhibition patterns across isozymes and related enzymes, where the enzymes share a common functionality at the active site, allelic proteins, binding to a family of ligands, etc. Thus, the library is useful as a tool for drug discovery, i.e., it is a means to discover novel lead compounds by screening the library against a variety of biological targets, and also as a tool for the development of structure-activity relationships in large families of related compounds.

Moreover, at page 17, paragraph 77, the specification reads as follows:

> The combinatorial libraries of the present invention may be screened for pharmacologically active compounds, including analogs, that is compounds that can affect the biological status of a biological system, usually a cellular system. The biological system will depend on the use of a biological source that will include cells and/or viruses. By pharmacologically active is meant that a compound may effect the function of a protein, e.g, an enzyme, including physiological process such as signal transduction by a cellular receptor, initiation, cessation or modulation of an immune response, modulation of heart function, nervous system function, or any other organ or organ system. A pharmacologically active compound may also stimulate or inhibit the activity of a bacteria, virus, fungus, or other infectious agent. A pharmacologically active

> compound may modulate the effects of a disease, that is prevent or decrease the severity of or cure a disease such as cancer, diabetes, atherosclerosis, high blood pressure, Parkinson's disease and other disease states. Screening for pharmacological activity may be performed by assays as would be known in the art, depending on the function or activity to be assessed.

In addition, at page 31, paragraph 111, the specification reads as follows:

> In the case of affinity labels, one can determine the available activity in a protein composition of the target proteins, one can differentiate the activity between the target protein and other members of the class on the properties of the protein composition, e.g. cell(s) or lysate, one can obtain a protein activity profile for tissue, cells or lysate in response to various stimuli and one can screen compounds for their binding affinity to the target protein, e.g. drug screening.

Thus, when claims 1-3, 5, and 6 are considered in view of the specification, those skilled in the art readily recognize that the specification contains sufficient written description for methods for screening for the bioactivity of a candidate compound.

Furthermore, Applicants respectfully disagree with the Examiner's assertion that the rejected claims contain "no identifying characteristics . . . with respect to the type of 'active target members' (e.g., the specific type of protein or the protein sequence) or . . . a common functionality for the conjugation of the probe and the active target members (e.g., the sequence for the binding site of the 'active target members' to the probe) and the probes specific to the active target members," citing *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1405 (1997). In response to this assertion, Applicants respectfully direct the Examiner's attention to *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406 :

"The written description requirement may be satisfied through sufficient description of a representative number of species..." (emphasis added).

Moreover, it is submitted that an adequate description of a "representative number of species" does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces. *In re Bell,* 991 F.2d 781, 785 26 USPQ2d 1529, 1532 (Fed. Cir. 1993) With respect to the active target members set forth in the specification, it is submitted that the specification clearly describes a "representative number of species" to demonstrate that Applicants were in possession of the claimed active target members.

It is well-established that claims are to be interpreted in light of the specification (*AFG Industries, Inc. v. Cardinal IG Co., Inc.,* 239 F.3d 1239, 57 USPQ 2d 1776 (Fed. Cir. 2001) The specification contains more than sufficient guidance with respect to the identifying characteristics of "active target members." For example, at page 16, paragraph 74, the specification describes examples of target proteins, as follows:

> Exemplary protein targets described herein include enzymes, included in the groups oxidoreductases, hydrolases, ligases, isomerases, transferases, and lyases and include such enzymes or enzyme groups as serine hydrolases, metallo-hydrolases, dehydrogenases, e.g. alcohol and aldehyde dehydrogenases, and nucleotide triphosphate (NT)-dependent enzymes, although, the invention envisions ABPs which recognize any protein, e.g., enzyme, family. Other proteins include proteins that bind to each other or to nucleic acids, such as transcription factors, kringle structure containing proteins, nucleic acid binding proteins, G-protein binding receptors, cAMP binding proteins, etc.

Similarly, at page 17, paragraph 75, the specification provides, "Targets of interest will be particularly enzymes, other proteins include receptors, transcription factors, G-proteins, and the like." See also, page 32, paragraph 114, where the specification describes various types of enzymes that may serve as target proteins:

> Enzymes typically fall within six main classes including oxidoreductases, transferases, hydrolases, lyases, isomerases and ligases. In a particular

embodiment illustrated herein, an enzyme group of interest includes the class of hydrolases. One genus of the class is serine hydrolases, which includes sub-genera such as proteases, e.g.trypsins, chymotrypsins, esterases, such as acetylcholinesterases, thioesterases, amidases, such as FAAH, and acylpeptide hydrolases, lipases, transacylases, such as lecithin:cholesterol acyltransferase. Another sub-genus is cysteine hydrolases, such as caspases, cathepsins, and palmitoyl acyltransferases. Another sub-genus is metallohydrolases, including matrix metalloproteinases ("MMPs"), e.g. MMP1 – 13, membrane type metalloproteinases, aminopeptidases, and ADAMalysins. In addition, are phosphatases, such as alkaline phosphatases, acid phosphatases, protein tyrosine phosphatases, and serine/threonine phosphatases. Further included are the GTPases and ATPases. Besides hydrolases are kinases, which include enzymes such as tyrosine kinases, e.g. src, abl, and lck, serine/threonine kinases, e.g. MAP kinases, MAPK kinases, CAM kinases, protein kinase C, and casein kinases. Also of interest are oxidoreductases, such as cytochrome P450s, amine oxidases, alcohol dehydrogenases, aldehyde dehydrogenases, such as ALDH1, ALDH2, ALDH3, desaturases, etc. Other proteins that are of interest include receptors, such as HLA antigens, hormone receptors, G-proteins coupled receptors, ion channels, transcription factors, protein inhibitors and the like.

Additionally, the specification describes what is meant by "related group of proteins," that is, proteins that perform the same activity, and provides examples. See, for example, page 26, paragraph 100:

The probe may be specific for a single protein or more usually a related group of proteins. By related group of proteins is intended proteins that perform the same activity, as with enzymes that belong to the same group and catalyze the same reaction, e.g. hydrolysis, phosphorylation, oxidation, etc., and usually having one or more of the following characteristics: the same functionality at the active site; the same spatial orientation of functional groups that bind to the ligand; similar

> spatial structure and conformation; similar molecular weight; the same or similar cofactors or complexing proteins; and similar function. To enhance the distinction between active proteins and inactive proteins, special chemically reactive groups are employed.

Thus, claims 1-3, 5, and 6, when interpreted in light of the specification, adequately describe what is meant my "active target members."

The specification also adequately describes what is meant by "a common functionality for the conjugation of the probe and the active target members." Because the ABPs employed in the claimed methods label proteins in an activity-dependent manner, those skilled in the art recognize that each ABP will vary depending upon the target protein(s) chosen for activity-based analysis. It is respectfully submitted that the ability to label proteins in an activity-dependent manner is a readily identifiable characteristic that, combined with the abundant information provided with respect to selection of target proteins and characterization of functional groups of activity-based probes directed to various target proteins, is sufficient to demonstrate possession of the claimed invention. The specification provides, for example, at page 19, paragraph 81, that "a functional group (F) . . . specifically and covalently bonds to the active site of a protein." The specification also provides examples of particular functional groups, for example, at page 19, paragraph 83:

> Exemplary Fs as used in an ABP of the invention include an alkylating agent, acylating agent, ketone, aldehyde, sulphonate or a phosphorylating agent. Examples of particular Fs include, but are not limited to fluorophosphonyl, fluorophosphoryl, fluorosulfonyl, alpha-haloketones or aldehydes or their ketals or acetals, respectively, alpha-haloacyls, nitriles, sulfonated alkyl or aryl thiols, iodoacetylamide group, maleimides, sulfonyl halides and esters, isocyanates, isothiocyanantes, tetrafluorophenyl esters, N-hydroxysuccinimidyl esters, acid halides, acid anhydrides, unsaturated carbonyls, alkynes, hydroxamates, alpha-halomethylhydroxamates, aziridines, epoxides, or arsenates and their oxides.

Sulfonyl groups may include sulfonates, sulfates, sulfinates, sulfamates, etc., in effect, any reactive functionality having a sulfur group bonded to two oxygen atoms. Epoxides may include aliphatic, aralkyl, cycloaliphatic and spiro epoxides, the latter exemplified by fumagillin, which is specific for metalloproteases.

Additionally, the specification provides guidance on the selection of an appropriate functional group for protein target, for example, at page 27, paragraph 101:

A "chemically reactive group" is a moiety including a reactive functionality that does not react efficiently with the generally available functional groups of proteins, e.g. amino, hydroxy, carboxy, and thiol, but will react with a functionality present in a particular conformation on a surface. In some situations the reactive functionality will serve to distinguish between an active and an inactive protein. In other situations, the conformation of the chemically reactive group will bind to the specific conformation of the target protein(s), whereby with a slowly reactive functionality or one that requires activation, the predominant reaction will be at the active site. For example a photoactivatable group may be used such as a diazoketone, arylazide, psoralen, arylketone, arylmethylhalide, etc. any of which can bind non-selectively to the target protein, while the probe is bound to the active site. Olefins and acetylenes to which are attached electron withdrawing groups such as a sulfone, carbonyl, or nitro group may be used to couple to sulfhydryl groups.

The specification provides much guidance with respect to the selection of "active target proteins." For example, the specification provides at page 31, paragraph 113:

For many of the enzyme genera, functionalities are known that do not significantly react with enzymes of other genera, particularly non-enzymatic proteins and enzymes that have different reactive sites. It is also desirable that the

> functionality does not react with inactive target enzyme. Examples of inactive states include: 1) proenzymes, e.g. requiring cleavage of the protein; 2) enzymes bound by endogenous inhibitors (either covalent or non-covalent); 3) enzymes in an inactive conformation (e.g. enzymes that require the binding of another protein, a conformational change, covalent modification by phosphorylation/reduction/oxidation/methylation/acylation (e.g. formic or acetic acid) for conversion to an active state; 4) denatured enzymes; 5) mutant enzymes; 6) enzymes bound by either reversible or irreversible exogenous inhibitors; and 7) enzymes requiring a cofactor for activity. The enzymes of interest will usually have at least one of serine, threonine, cysteine, histidine, lysine, arginine, aspartate or glutamate as a member of the active site involved in the catalysis of the enzyme reaction. One or more of the functionalities of these amino acids may be the target of the ABP. The manner in which the inactive enzyme is inactivated is chosen to emphasize the differences in bonding of the ABP between the active and inactive state.

Thus, the specification provides adequate guidance for selection of common functionalities.

Applicants also respectfully disagree with the Examiner's assertion that "specification description is directed to the syntheses of a specific probe (e.g., the biotinylated fluorophosphonate probe such as FP-biotin and FP-peg biotin) that have specificity toward an "active target member" (e.g., serine hydrolases). As noted above, the specification clearly sets forth a wide variety of proteins contemplated for use in the practice of the invention and sets forth (for exemplary purposes only) activity-based quantitation and determination of the serine hydrolases (see specification, Example 4). In addition, the specification describes several sulfonate ester activity-based probes (see, for example, Example 7) . Applicants respectfully point out that particular examples of ABPs set forth in the Examples are merely illustrative and not intended to be limiting.

It is respectfully submitted that Applicants are entitled to claims drawn as broadly as the prior art will allow. The activity characteristics set forth in the present claims are the most appropriate descriptions known to Applicants to describe the methods of the present invention. Thus, it is submitted that the specification "clearly allows persons of ordinary skill in the art to recognize that he or she invented what is claimed." *Union Oil Co. of California v. Atlantic Richfield Co.* 54 USPQ2d 1227 (2000)

Applicants submit that the present specification contains a complete description of the invention sufficient to enable a person skilled in the art to utilize the methods of the invention. Accordingly, it is respectfully submitted that the rejection of claims 1-3, 5, and 6 under 35 U.S.C. § 112, first paragraph, as allegedly lacking adequate written description, is not properly applied. Reconsideration and withdrawal of the rejection are therefore respectfully requested.

B. Rejection Under 35 U.S.C. § 112, Second Paragraph

The rejection of claims 1-3, 5, and 6 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention, is respectfully traversed.

With specific reference to the phrase "condition for reaction" as recited in claim 1, it is submitted that this phrase is clear and unambiguous as written. The "conditions for reaction" are those conditions that allow for an interaction between a given probe and given target proteins. Upon review of the specification, these conditions are readily apparent to those skilled in the art. For example, in the specification, paragraphs 159, 167, 174, and 180 all describe various "conditions for reaction." In view of this disclosure, it is submitted that those skilled in the art can readily identify "conditions for reaction", and therefore there is no ambiguity with respect to this phrase as it is used in claim 1.

With specific reference to the term "untreated" as recited in claim 1, it is submitted that this term is clear and unambiguous as written. When this term is considered in view of the specification, those skilled in the art readily recognize the intended meaning of this term. For example, the specification at page 28, paragraph 104, reads as follows:

> "...information from studies with ABPs is preferable if one compares the level of protein conjugates in a portion of the sample that has been *treated with inactivating conditions* to a portion of the sample that contains active, wild-type or *untreated* proteins. (emphasis added)

Clearly, the term "untreated" refers to proteins that have not been treated with inactivating conditions. The ability to inactivate proteins is well within the level of skill in the art, and there are a variety of well-known methods for inactivating proteins. Thus, it is submitted that skilled artisans, when considering the term "untreated" as used in claim 1, can readily determine the scope of the invention.

Similarly, the term "inactivated" as recited in claim 1, is also clear and unambiguous as written. "Inactivated" refers to proteins whose three-dimensional structures have been altered, thereby inactivating an active site of the protein. The probes described in the present invention are activity based probes (ABPs). Thus, the manner in which an inactive protein is inactivated is chosen to emphasize the differences in bonding of the ABP between the active and inactive state. Those skilled in the art can readily identify several methods for inactivating a protein, such as for example by applying heat, as set forth in claim 6. Moreover, the specification clearly describes how a comparison between an activated protein mixture and an inactivated protein mixture is to be carried out (see specification, page 34, paragraph 119):

> A portion of each sample is treated so that the active proteins in the one portion are inactivated. Protein portions of the active and inactive samples are then treated with isotopic variants of the same ABP (e.g., one variant contains 5-

10 hydrogens (light probe) and is applied to the inactive portions, the second variant has these 5-10 hydrogens substituted with deuteriums (heavy probe) and is applied to the active portions). After sufficient reaction time, the inactive and active portions of each sample are then separated from their respective ABPs (e.g., by gel filtration chromatography), combined to form a mixed sample, and this mixed sample is digested with a protease (e.g., trypsin) to create a mixture of peptides. These peptides are then treated with an affinity support to selectively isolate peptides covalently tagged with an ABP (e.g., avidin is the affinity support if the probe's tag is biotin). The isolated peptides are then optionally separated by a liquid chromatography step (e.g. HPLC) and characterized by mass spectrometry. ABP-tagged peptides representing active proteins are defined as those found in significantly greater excess (e.g., at least three-fold greater in mass ion abundance) bonded to the heavy probe than to the light probe.

With specific reference to the term "mixture", as recited in claim 1, Applicants respectfully disagree with the Examiner's assertion that there is allegedly no antecedent basis for this term. The term "mixture" first occurs in line 2 of claim 1, and it is clear that this provides antecedent basis for the later occurrences of this term in claim 1.

With specific reference to the term "combining" as recited in claim 1, it is submitted that this term is clear and unambiguous as written. As set forth above, the specification clearly sets forth (see page 34, paragraph 119) that "combining" refers to combining at least one probe with an untreated portion of a proteomic mixture and combining at least one probe with an inactivated portion of the proteomic mixture. Thus, when this term is considered in view of the specification, skilled artisans can readily understand the intended meaning of the term in question.

With specific reference to the definition of "F" in claim 1, it is submitted that this issue is rendered moot by correction of a typographical error in claim 1. Specifically, the

second occurrence of the variable "F" in claim 1 at line 12 has been corrected to recite "R" instead.

With reference to the method set forth in claim 1, Applicants respectfully disagree with the Examiner's assertion that the method is incomplete for allegedly omitting essential steps. Contrary to the Examiner's assertion, the method of claim 1 clearly states "...comparing the amount of each of the proteins sequestered from the untreated portion and the inactivated portion as indicative of the bioactivity of said candidate compound with said target proteins". Those skilled in the art recognize that it is this comparison that correlates the bioactivity of a candidate compound with a group of target proteins. Indeed, it is submitted that the method step suggested by the Examiner is not required to practice the invention as set forth in claim 1. Thus, the method set forth in claim 1 is complete as written, and requires no additional steps.

With specific reference to the use of the term "enzymes" in claims 2 and 3, Applicants respectfully disagree with the Examiner's assertion that there is allegedly insufficient antecedent basis for this term in claim 1. Contrary to the Examiner's assertion, claim 1 at line 10 recites "a target enzyme." It is submitted that this provides sufficient antecedent basis for the recitation of "enzymes" in claims 2 and 3.

For all of the reasons set forth above, it is respectfully submitted that the rejections of claims 1-3, 5, and 6 under 35 U.S.C. § 112, second paragraph, are not properly applied. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

C. Rejection Under 35 U.S.C. § 103(a)

The rejection of claims 1, 2, 5, and 6 under 35 U.S.C. § 103(a), as allegedly being unpatentable over Gygi et al. (*Nature Biotechnology* , 1999, 17(10):994-999) and Liu et al. (*PNAS*, 1999, 96(26):14694-14699), is respectfully traversed. Applicants' invention,

as defined for example, by claim 1, distinguishes over Gygi et al., by requiring a method for screening for the bioactivity of a candidate compound toward a group of related target proteins in a proteomic mixture of proteins from a cell, employing at least one well-defined probe, wherein the method includes combining at least one probe with an untreated portion of a proteomic mixture and with a portion inactivated with a non-covalent agent under conditions for reaction with target proteins; sequestering proteins conjugated with the probe from each of the mixtures; determining the proteins that are sequestered; and comparing the amount of each of the proteins sequestered from the untreated portion and the inactivated portion as indicative of the bioactivity of the candidate compound with said target proteins.

The present invention describes screening methods employing probes that are able to record variations in protein activity, rather than merely level of protein expressed in a cell. Gygi et al. is silent with respect to screening methods employing probes that are able to record variations in protein activity. Indeed, Applicants respectfully disagree with the Examiner's assertion that Gygi et al. describes "...comparing the amount of each of the proteins sequestered from the untreated portion and the inactivated portion as indicative of the bioactivity of the candidate compound with said target proteins", as recited in present claim 1. It is submitted that Gygi et al. can not accomplish this "comparing" requirement since Gygi et al. does not employ the well-defined, activity based probes set forth in the present invention. Instead, Gygi et al. merely describes a method for quantifying individual proteins in a mixture, regardless of the level of protein activity in the mixture. In addition, the protein mixture described in Gygi is denatured, wherein all protein structure and activity has been destroyed. Thus, Gygi's probes react with all available reaction sites on all proteins in the mixture. In contrast, the probes set forth in the present invention react with an active site of a protein. Accordingly, it is respectfully submitted that Gygi et al. does not disclose or suggest the methods of the present invention.

Moreover, Applicants respectfully submit that Liu is not available as prior art under 35 U.S.C. 103(a) since the subject matter set forth in Liu was derived from Applicants' own work. Indeed, it is noted present inventors Cravatt and Patricelli are co-authors of the Liu publication, and as set forth in the declaration filed in co-pending Application No. 09/738,954 (attached hereto as Exhibit A), co-author Liu did not contribute to the mental conception of the present invention. Accordingly, reconsideration and withdrawal of the rejection of claims 1, 2, 5, and 6 under 35 U.S.C. § 103(a) are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, reconsideration and favorable action on all claims are respectfully requested. In the event any matters remain to be resolved, the Examiner is requested to contact the undersigned at the telephone number given below so that a prompt disposition of this application can be achieved.

Respectfully submitted,

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